Radiogenomics of Lung Cancer and Image guided Video Assisted Thorascopic Surgery

Background and Significance:

Approximately 1,000,000 lung nodules and other abnormal lesions such as GGO (ground glass opacities) are detected in people in the United States each year. In reported studies, up to 51% of smokers aged 50 years or older have pulmonary nodules/lesions on CT scans.

Recently, a large prospective randomized trial demonstrated that screening patients at risk for lung cancer based on age and smoking history with chest computed tomography (CT) reduces the mortality from lung cancer (7,8). The National Lung Screening Trial (NLST) involving more than 53,000 heavy smokers resulted in 20 percent fewer lung cancer deaths among trial participants who met specific criteria and were screened with low-dose helical CT (9). As a consequence of this positive study, it is expected that hundreds of thousands of patients with lung nodules/lesions will come to surgical biopsy. Statistically, the majority of these people will have benign diseases, but definitive diagnosis will be required in those with sufficiently large lesions. Furthermore, patients with very small lesions (<<1cm) that are suspicious for cancer will be discovered that are challenging to resection using current surgical techniques. Thus new protocols are required to improve resection accuracy, preserve normal lung and reduce morbidity, mortality and costs to society.

Based on clinical circumstances, lesions discovered on CT screening may be followed up radiographically or patients may be referred for biopsy, radiological or surgical. The decision tree is based on size, appearance and clinical scenario (true for lesions suspected of either malignant or non-malignant etiologies), hence the need to develop image based phenotype with correlation to genomic and prognostic factors.

Screening with computed tomographic (CT) scans has to some degree changed the technologies available for surgery for both lung cancers and for benign diseases. In the past and for most cases in the US currently (>75%), most lung cancers were relatively large and patients required open thoracotomy for resection. Now-a-day, many cancers are much smaller and can be accessed through minimally invasive approaches, Video Assisted Thoracic Surgery (VATS) (10). This is particularly the case in specialized centers such as BWH where most Thoracic Surgeons will attempt VATS resection for the majority of pulmonary nodules for any etiology. The same applies to non-cancerous nodules that need to be biopsied or resected for diagnosis and/or treatment. This surgery is routinely performed through 3 small incisions (1cm or so each) whereby one incision is used for the placement of a rigid video telescope camera and the other incisions are used to grab and mobilize the lung, bring it closer to one incision which will allow palpation of the lung with a finger tip to identify the nodule/lesion that will then be cut out using a stapling device.

The crux of the challenge and the reason for this protocol is that it is very hard to define histological and prognostic character based on image alone and at surgery: many of these nodules/lesions are hard to palpate and to precisely define their location for resection. This is particularly true for smaller nodules or GGOs, precisely the ones that require resection to provide early diagnosis and therapy since at least half may be benign. Thus, using current non-image guided technologies result in three potential non-ideal outcomes: 1. A more extensive resection of normal lung parenchyma (such as lobectomy or segmentectomy) to make sure that the lesion is included even if it is non-palpable; 2. An enlargement of at least one incision to insert the hand into the chest for better physical definition-resulting in a more painful and complex recovery for the patient with resulting longer recovery, chronic pain and greater cost; 3. Too close a surgical margin to the cancer requiring re-operative surgery of increasing the chance of recurrence.

The concept of intra-operative imaging-guidance is not new and has been used for breast biopsy (needle localized breast biopsy) for many decades and more recently for neurosurgery. The AMIGO suite at BWH is an innovative operating room that allows for concurrent radiological imaging. It has a centralized, fully equipped and credentialed operating room with all the amenities as well as a fluoro-CT, movable MRI, Focused US and a PETCT area. The AMIGO suite is unique NIH funded resource for developing and perfecting novel surgical procedures which require imaging support. The intention is to develop these types of procedures in the AMIGO suite and then to modify them so that the successful procedures may be performed in the operating rooms. Parenthetically, an identical fluoro-CT is also available in one of the BWH operating rooms.
Our goal in this protocol is to enroll patients who require VATS for specified lung lesions, have the patient be operated in the AMIGO suite where they undergo the following process: intubated with a double lumen tube, positioned in the lateral decubitus position, undergo CT-fluoroscopy to confirm the location of the nodule, perform image guided needle biopsies and mark the lesion by placing a needle guided T-bar device. At this point, VAT surgery will be performed to resect the lung lesion utilizing the marking, which will remove the T-bar with the specimen. The specimen will then be removed in an Endo-bag and submitted for a quick CT picture (away from the patient) and sent for pathological analysis. Only the underlined elements are experimental, the operation itself and indications are standard of care. The intentions are to define the methodology, risks, exposure etc. and then work in follow-up trials to potentially improve upon the marking device and the procedure to get them to the point where this approach is available for any patient undergoing lung resection. We believe that this is a game changing approach and will help guide surgery and help us do radiogenomic analysis of early lung cancer and in the long term help develop an image based biomarker.

The purpose of this clinical study is to develop image based phenotypes by correlating with cytological and genomic information prior to excision in the Advanced Multimodality Image Guided Operating (AMIGO). Our hypothesis is that an effective marking strategy of 2cm or smaller lung lesions, using intra-operative imaging-guidance, will enable accurate and efficient lesion resection while preserving as much as possible of the normal lung parenchyma by limiting the resection to the lesion and its immediate surroundings. Our clinical initiative has 2 specific aims.

**Aim 1:** To correlate imaging features and determine whether molecular analysis of the lesion/nodule in conjunction with cytological analysis using FNAs (Fine Needle Aspirations) just prior to resection can predict diagnosis and prognosis, thus enable the development of an imaging biomarker and phenotype signature of early Lung Cancer.

**Aim 2:** To optimize the placement of fiducials to enable image guided VATS (Video Assisted Thoracoscopic Surgery) resection using real-time anatomical imaging modality for lung lesions/nodules.

**Patient cohort and clinical question**

Patients with less than 2cm lung nodules/lesion being referred to thoracic surgery for resection.

**Imaging modalities**

CT scans.
Advanced Multimodality Image Guided Operating (AMIGO), with a Dyna CT scan and fluoroscopic facility.

**Patient flow:** Referred from Thoracic Surgery.

**Reference standard information, for studies of diagnosis or prediction**

Preclinical feasibility study with 25 patients with lesions lesion than is currently underway.

**d. Data Collection and Analysis:**

- Image characteristics-solid, cavitary, air brochograms, margins, pleural tags, GGO or solid, GGO component
- Histological diagnosis, Genomics, Time for fiducial placement, biopsy and resection, Surgical margins, Time to recurrence, Overall survival. Interim analysis at 12 months, 24mths and at 3 years. Exploratory analysis will be performed, Logistic regression and Linear regression analysis will be performed.

**e. Feasibility:**

The pilot study is currently underway and there is full departmental support from both Radiology and Thoracic Surgery to get the protocol implemented.